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(54) Valproic and (E)-2-valproenoic acid derivatives, processes for the preparation thereof and pharmaceutical compositions therefrom.

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EP-A- 0 114 720
EP-A- 0 133 218
AT-B- 365 164
DE-A- 2 317 219
DE-A- 2 413 803
DE-C- 2 421 537
GB-A- 2 010 267

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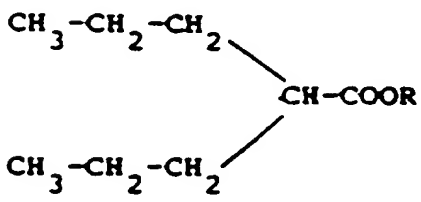
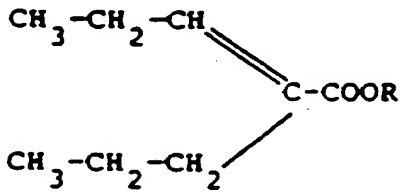
Description

The present invention relates to 2-propyl-2-pentanoic acid (valproic acid) esters of formula (I):



(I)

and (E)-2-propyl-2-pentenoic acid (E)-2-valproenoic acid esters of formula (II)



(II)

wherein R is an alkoxyalkyl, alkanoyloxyalkyl, aroyloxyalkyl, alkoxycarbonyloxyalkyl, aralkenoyloxyalkyl group, a mono- or bicyclic heterocycloalkyl group, which may be saturated or unsaturated and optionally substituted with a C_1-C_4 alkyl group or an oxo group; the above cited alkyl, alkoxyl and alkanoyl groups having straight or branched chain and containing 1 to 10 carbon atoms.

In formulae I and II, R preferably represents 2-methoxyethyl, 2-isopropoxyethyl, 2-butoxyethyl, 1-methyl-2-methoxyethyl, acetoxymethyl, 2-acetoxyethyl, pivaloyloxymethyl, 1- and 2-pivaloyloxyethyl, 2-propyl-pentanoyloxymethyl, 2-propyl-pentenoyloxymethyl, 2-(2-propyl pentanoyloxy)ethyl, 2-(2-propyl-pentenoyloxy)ethyl, 1-ethoxycarbonyloxyethyl, 2-benzoyloxyethyl, 2-(3,4,5-trimethoxylbenzoyloxy)ethyl, 2-cinnamoyloxyethyl, 2-phthalidyl, 2-(N-succinimido)ethyl, (5-methyl-2-oxo-1,3-dioxolene-4-yl)methyl, 2-pyridylmethyl.

The following compounds: pivaloyloxymethyl 2-propylpentanoate, described in CH Pat. n. 635062 and in AT-B-365164, 1-ethoxycarbonyloxyethyl 2-propylpentanoate, described in EP 114720 and pyrrolidin-1-yl methyl 2-propylpentanoate, described in DE-2317219 are specifically excluded from the present invention.

Valproic acid is an anticonvulsivant drug that has been widely used for a long time, as such or as sodium salt, in the treatment of epilepsy. In spite of its tested clinical efficacy, the compound actually presents serious side effects; that often prevent its use in the therapy. Valproic acid has been in fact associated with two kind of rare but extremely dangerous reactions, such as a serious hepatic insufficiency and teratogenic effects.

Another factor limiting the use of the drug is its kinetic profile, deriving from the particular chemicophysical characteristics of the compound.

As a matter of fact, valproic acid has a quite short half life that, besides causing consistent fluctuations in the plasmatic levels of the active ingredient, also involves a high number of daily administrations of drug (from a minimum of 3.4 to a maximum of 6 administrations/die).

The drawbacks caused by the therapy with valproic acid have stimulated more and more the search for new solutions in the last few years.

This research has aimed at obtaining new salts of the compound, in order to improve its stability in pharmaceutical compositions of pro-drugs of the active principle, in order to improve its bioavailability and to prolong its effect.

Among the numerous derivatives that have been obtained so far, the only one that seems to be a valid alternative to the starting compound is its main active metabolyte, trans-2-ene-valproic acid or 2-propyl-pentenoic acid, that proved to have a wide spectrum anticonvulsivant activity, a potency and a duration of action comparable to those of valproic acid, and remarkably reduced toxic effects.

Trans-2-ene-valproic acid is in fact totally devoid of teratogenic effects, and it is much better tolerated

at hepatic level, thanks to a remarkably reduced hepatic concentration in comparison with valproic acid, after oral administration of equimolecular doses of the two active principles.

The pharmacokinetic behaviour of trans-2-ene-valproic acid is similar to the one of valproic acid.

The half life in man is slightly higher than that of the starting compound (12.5 hours in comparison with 9-10 hours of valproic acid), so that, for its use in the therapy, there are the same drawbacks of valproic acid.

It has now been found, and it is one of the objects of the present invention, that new esters of valproic acid and of valproenoic acid are surprisingly endowed with particularly favourable characteristics, since they exhibit an anticonvulsivant and antiepileptic activity that can be compared with that of valproic acid, together with a better bioavailability and a remarkably reduced toxicity.

Thanks to these characteristics, the new derivatives of formula (I) and (II) may therefore be effectively used in the therapy of epileptic disorders.

Novel compounds of formulae I and II may be prepared by reacting the starting compound , i.e. valproic acid (formula I, R = H) or (E)-2-valproenoic acid (formula II, R = H) with at least an equivalent molar amount of a haloderivative of formula RX, wherein R has the above defined meanings and X is preferably chlorine or bromine.

The reaction is usually carried out in an inert organic solvent which does not negatively affect said reaction, in the presence of a suitable amount of an appropriate standard alkali substance and of a catalyst.

The reaction is generally effected at a temperature ranging from about 0 °C to the solvent's boiling temperature, for a time from about 0,5 to about 24 hours.

Although any inert organic solvent may be used, aprotic polar organic solvents such as dimethylformamide, acetone, dioxane, tetrahydrofuran are generally preferred.

Among the appropriate standard alkali substances which may be used in the process, there are alkali and alkali-earth metal oxides, bicarbonates and carbonates, such as magnesium oxide, potassium bicarbonate, sodium bicarbonate, potassium carbonate and magnesium carbonate, and also tertiary amines such as triethylamine, N,N-dimethylaniline and pyridine; potassium carbonate being preferred.

The employed standard alkali substance must be present in a sufficient amount to neutralize the halohydric acid which is formed during the reaction.

Alkali and alkali-earth metal iodides may be used as catalysts in the reaction, potassium iodide being preferred.

According to an alternative process, valproic and (E)-2-valproenoic acid chlorides may be treated with the corresponding alcohol derivatives of the kind ROH, wherein R has the above defined meanings.

In this case, the reaction is carried out under conditions similar to those of the above process, of course avoiding the use of protic solvents.

Alifatic or aromatic tertiary amines may be used to play the role of both solvent and base to neutralize the halohydric acid which is formed during the reaction.

A third particularly advantageous process to obtain alkylidene-bis-valproates or alkylidene-bis-(E)-2-valproenates (compounds of formula I or II wherein R is $-CH_2-O_2CCH(C_3H_7)2$ or $-(CH_2)_2-O_2CCH(C_3H_7)_2$, consists in treating valproic or (E)-2-valproenoic acids with an alkyl dihalide of the type $X-(CH_2)_n-X$, (wherein n = 1-5 and X = Cl, Br, I).

The reaction is carried out in a biphasic system consisting of an alkali aqueous solution of the starting compound and of the alkyl dihalide, which plays the double role of reagent and solvent, in the presence of an appropriate catalyst.

The reaction is generally carried out at a temperature from 10° to 70 °C, for a time ranging from 1 to 24 hours.

Inorganic bases such as alkali and alkali-earth metal hydroxides, oxides, bicarbonates and carbonates, for example sodium hydroxide, potassium hydroxide, sodium bicarbonate, potassium carbonate, magnesium carbonate, may be employed as alkali substances.

As catalysts, quaternary alkylammonium salts, such as tetraethylammonium bromide, tetrabutylammonium hydrogenosulfate, tetrabutylammonium iodide, etc. are particularly preferred.

In order to promote the reaction, alkali or alkali-earth metal iodides may be further used, preferably potassium iodide. The starting materials necessary for preparing the derivatives object of the present invention are commercially available or may be prepared according to methods known in the literature.

Some non-limiting examples of the processes for preparing the compounds of the invention are reported hereinbelow.

EXAMPLE 1

2'-Acetoxyethyl 2-propyl-pentanoate (valproic acid 2-acetoxyethyl ester) (compound n. 3)

20.18 g (0.14 mole) of 2-n-propyl-pentanoic acid (valproic acid) were dissolved in 150 ml of dimethylformamide. After heating to 70-100 °C, 13.82 g (0.1 mole) of potassium carbonate were added. The mixture was stirred for about 10 minutes, then 1.66 g (0.01 mole) of potassium iodide followed by 17.16 g (0.14 mole) of 2-acetoxyethyl chloride were added dropwise. Stirring was continued for about 3 hours at 80-100 °C, then the mixture was left to cool to room temperature and about 600 ml of water were added. The mixture was extracted with ethyl acetate and the organic layer was washed with a sodium bicarbonate saturated solution, then with water till neutral.

The organic solution was dried over sodium sulfate and the solvent was evaporated off under vacuum, in rotary evaporator.

The residual oil was fractionally distilled under vacuum, to yield a fraction distilling at 83 °C at 0.1 mbar.

22.57 g of compound (70% yield) were obtained.

MF = $C_{22}H_{22}O_4$ MW = 230.308

Elemetal analysis and spectroscopic data (IR, NMR) confirm the structure of the compound.

By the same procedure, again using 2-propyl-pentanoic acid as the starting material, compounds n. 4 to n. 8, were obtained, whose characteristics are reported in table 1.

Analogously, but starting from 2-propyl-2-pentenoic acid, compounds n. 9 to n. 14 were obtained, whose characteristics are reported in table 2.

EXAMPLE 2

2-(2-propylpentanoyloxy)ethyl 2-propylpentanoate (oxyethylene valproyl-valproate) (compound n. 15)

176.58 g (0.520 mole) of $(C_4H_9)_4N^+HSO_4$ and subsequently 800 ml of 1,2-dichloroethane were added to a solution of 150 g (1.040 mole) of 2-propyl-pentanoic acid (valproic acid) in 110.22 ml (1.092 mole) of 30% NaOH. After heating to reflux (T = 74 °C), 18.13 g (0.109 mole) of KI were added, keeping reflux for 20 hours. After cool ing to room temperature, the two phases were separated and the aqueous layer was extracted with about 300 ml of 1,2-dichloroethane. The 1,2-dichloroethane solutions were combined, washed many times with water, then with 10% NaOH and again with water till neutral. The organic phase was washed many times with 0.5 N HCl, then with water till neutral.

The mixture was dried with Na_2SO_4, filtered, decolorized with bleaching clay, filtered and the solvent was evaporated. The obtained oil was treated with ethyl ether, and the solid part was removed by filtration. Solvent was evaporated off. The residual oil was subjected to distillation under vacuum and the fraction distilling at T = 93 °C at pression = 1mbar was recovered.

71.51 g of compound (43.73%) were obtained.

M.F. = $C_{18}H_{34}O_4$ M.W. 314.47

Elemental analysis and spectroscopic data (IR, NMR) confirm the structure of the compound.

By a procedure similar to the one discribed in example 2, using valproic acid and methylene chloride as the starting compounds, compound n. 16, i.e. 2-propylpentanoyloxymethyl 2-propyl-pentanoate, was obtained, whose characteristics are illustrated in table 1.

EXAMPLE 3

Pivaloyloxymethyl 2-propyl-2-pentenoate (E cis) (valproenoic acid pivaloyloxymethyl ester) (compound n. 17)

13.82 g (0,1 mole) of K_2CO_3 were added to a solution of 14.22 g (0.1 mole) of (E)-2-propyl-2-pentenoic acid in 400 ml of acetone, heated to 40-50 °C, and subsequently 15.36 g (0.102 mole) of chloromethyl pivalate were added dropwise, during 10 minutes. The mixture was refluxed for about 3 hours and, after cooling to room temperature, 2 l of water were added. The mixture was repeatedly extracted with ethyl acetate, the combined organic layers were wached with a $NaHCO_3$ saturated solution, then with water till neutral.

After drying over Na_2SO_4, solvent was evaporated off to give an oily residue which was distilled under vacuum. The fraction distilling at 85 °C at 1.3 mbar was recovered.

18.71 g of compound (73% yield) were obtained.

M.F. = $C_{14}H_{24}O_4$ M.W. = 256.33

Elemental analysis and spectroscopic data (IR, NMR) confirm the structure of the compound.

By a procedure similar to the one described in example 3, again using (E)-2-propyl-pentenoic acid as the starting compound, compounds n. 18 to n. 21, whose characteristics are reported in table 2, were obtained.

EXAMPLE 4

2-(2',5'-dione-pyrrolidine-1-yl)ethyl 2-propyl-2-pentenoate (E cis) valproenoic acid 2-(N-succinimido) ethyl ester)

22.49 g (0.14 mole) of (E)-2-propyl-2-pentenoic acid chloride were slowly added to a solution of 19.75 g (0.138 mole) of 1-(2'-hydroxyethyl)-pyrrolidine-2,5-dione in 100 ml of pyridine heated at 35-45° C. The mixture was left at 40-50° C for about 1 hour, then 500 ml of water were added. The mixture was extracted repeatedly with ethyl acetate and the combined organic layers were washed with a $NaHCO_3$ saturated solution, then with water till neutral. After drying over Na_2SO_4 , solvent was evaporated and an oil was obtained which was distilled under vacuum. The fraction distilling at temperature 145° C at a 0.18 mbar pressure was recovered.

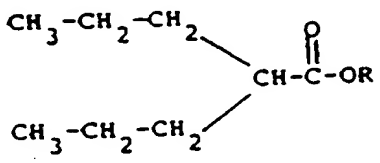
29.13 g of compound (78% yield) were obtained.

MF = $C_{14}H_{21}NO_4$ MW = 267.32

By a similar procedure, using (E)-2-propyl-2-pentenoic acid chloride and the corresponding hydroxyalkyl derivatives as the starting materials, compounds n. 23 to n. 27 were obtained, whose characteristics are reported in table 2.

TABLE 1

Compounds of formula:



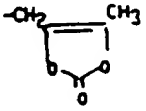
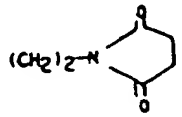
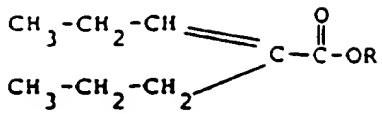
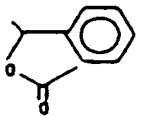
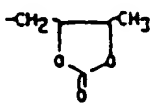
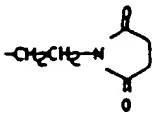
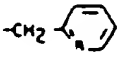
Comp.	R	B.P.°C/mbar	M.F.	M. W.	CHF
3	$-(CH_2)_2O_2C-CH_3$	83/0,1	$C_{12}H_{22}O_4$	230,308	1312
4	$-CH(CH_3)-O_2C-C(CH_3)_3$	80/0,1	$C_{15}H_{28}O_4$	272,37	1314
5	$-(CH_2)_2-O_2C-C(CH_3)_3$	106/0,1	$C_{15}H_{28}O_4$	272,37	1313
6	$-(CH_2)_2-O_2COC_2H_5$	100/0,1	$C_{13}H_{24}O_5$	260,32	1308
7		127/0,1	$C_{13}H_{20}O_5$	256,30	1315
8		132/0,2	$C_{14}H_{23}NO_4$	269,35	1359
15	$-(CH_2)_2-O_2CCH(C_3H_7)_2$	93/1	$C_{18}H_{34}O_4$	314,47	1352
16	$-CH_2-O_2CCH(C_3H_7)_2$	100/0,1	$C_{17}H_{32}O_4$	300,44	1355

TABLE 2

Compounds of formula:



Comp.	R	B.P.°C/mbar	MF	M. W.	CHF
9	$-(CH_2)_2-O_2C-Ph$	155/0,2	$C_{17}H_{22}O_4$	290,35	1406
10	$-(CH_2)_2-O_2C-CH=CH-Ph$	187/0,1	$C_{19}H_{24}O_4$	316,38	1408
11	$-(CH_2)_2-O_2C-Ph-3.4.5(OCH_3)_3$	207/0,3	$C_{20}H_{28}O_7$	332,42	1409
12	$-(CH_2)_2-O_2CCH_3$	102/0,2	$C_{12}H_{20}O_4$	228,28	1415
13	$-(CH_2)_2-O_2OC(CH_3)_3$	106/0,18	$C_{15}H_{26}O_4$	270,36	1413
14	$-(CH_2)_2-O_2COC_2H_5$	116/0,25	$C_{13}H_{22}O_5$	258,31	1414
17	$-CH_2-O_2C-C(CH_3)_3$	85/1,3	$C_{14}H_{24}O_4$	256,33	1378
18		170/0,4	$C_{16}H_{18}O_4$	274,30	1410
19	$-CH_2O_2CCH_3$	86/0,3	$C_{11}H_{18}O_4$	214,25	1416
20	$-CH(CH_3)-O_2CC(CH_3)_3$	62/0,3	$C_{15}H_{26}O_4$	270,36	----
21			$C_{13}H_{18}O_5$	254,27	1418
22		145/0,8	$C_{14}H_{21}NO_4$	267,32	1417
23	$-(CH_2)_2-O-(CH_2)_3CH_3$	84/0,1	$C_{14}H_{26}O_3$	242,35	1411
24	$-CH(CH_3)-CH_2-OCH_3$	63/0,1	$C_{12}H_{22}O_3$	214,30	1412
25	$-(CH_2)_2-OCH(CH_3)_2$	78/0,1	$C_{13}H_{24}O_3$	228,32	1407
26	$-CH_2-CH_2-O-CH_3$	67/0,1	$C_{11}H_{20}O_3$	200,27	1420
27		108/0,1	$C_{14}H_{19}NO_2$	233,30	1421

The compounds of formula I and II have been subjected to a preliminar toxico-pharmacological study.

Toxicity

The toxicity after single administration has been determined by the oral route in mice.
All the compounds showed an approximate LD_{50} value higher than 2000 mg/kg. according to interpola-

tion on Probits diagram.

Anticonvulsivant activity

The determination of the anticonvulsivant activity has been carried out by the pentetrazol convulsions test in mice.

Male Crl: CD-1 mice (Charles River-Italy) housed in standard conditions since at least 7 days and fasting (water ad libitum) for 18 hours before the test, were administered subcutaneously, in the dorsal area, with a 0,9% pentetrazole saline solution, in an amount of 10 ml/kg (90 mg/kg).

Immediately after the injection of the convulsivant agent, the animals were kept in single boxes and observed for 30 minutes for the appearance of clonic convulsion. The presence of possible deaths or neurotoxicity symptoms was moreover assessed before the pentetrazol injection.

For the evaluation of the anticonvulsivant activity, the ratio of protected animals versus controls was recorded and AUC values (% protection x hours), both total and relative to the 8-16 hours time interval from treatment, were determined by the trapezoid method in order to evaluate the persistance of activity in time.

The obtained results expressed as AUC values are reported in tables 3 and 4 concerning respectively the valproic acid derivatives and the (E)-2-valproenoic acid derivatives of the present invention.

As reference compound, sodium valproate has been used in the first group at the maximum administerable dose, and valproenoic acid in the second group.

TABLE 3

Anticonvulsivant activity of compounds of general formula I (valproic acid derivatives): AUC values (area under the curve showing the percent protection in time against the convulsivant agent).

Compounds	Code (CHF)	Dose		Protection from convulsions onset AUC (protection % x h)	
		mg/kg	mmol/kg	total	8-16 h
3	1312	1070	4.6	609	116
4	1314	1265	4.6	625	240
5	1313	1265	4.6	519	200
6	1368	1197	4.6	621	148
7	1315	1190	4.6	681	144
8	1359	1251	4.6	647	116
15	1352	1461	4.8	---	---
16	1355	1395	4.6	751	252
sodium valproate	---	506	3.1	351	24

TABLE 4

Anticonvulsivant activity of compounds of the general formula II (valproenoic acid derivatives) : AUC values.

Compounds	Code (CHF)	Dose		Protection from convulsions onset AUC (protection % x h)	
		mg/kg	mmol /kg	total	8-16 h
9	1406	1347	4.6	181	28
10	1406	1217	4.6	341	112
19	1416	994	4.6	208	58
22	1417	1420	4.6	240	28
27	1421	1101	4.6	122	58
valproenoic acid	----	592	4.2	264	36

The compounds of formula I and II exhibit a positive pharmacological interest.

All the valproic acid derivatives (table 3) proved to be remarkably more active than the starting compound with a remarkably longer persistance of the activity itself as showed by the increase of the AUC values inherent to prolonged periods (8-16 hours from treatment).

The valproenoic acid derivatives (table 4), although showing an anticonvulsivant activity comparable to that of the starting compound, as showed by the AUC values increase inherent to prolonged period, are generally characterized by a longer duration of action of the activity itself.

The two combined effects, decrease of the activity peak and prolonging of activity in time, have considerable therapeutic advantages, in that a longer duration of action is accompanied by a reduction of side-effects, particularly of the neurotoxic effects related to the presence of high blood levels of valproic acid.

Another object of the present invention is provided by pharmaceutical compositions which may be administered by oral route, to be used in therapy for the treatment of epileptic conditions, said compositions containing as the active ingredient one compound of formulae I or II, in combination with at least a pharmaceutically acceptable excipient.

Examples of said compositions, which may be prepared according to conventional methods, preferably consist in soft-gelatin capsules, in which the active ingredient is present dissolved in a vegetal or mineral oil, or hard-gelatin capsules, in which the active ingredient is present in admixture with a gelifying agent, such as for instance precipitated silica and fatty substances having melting point higher than 50-60 ° C.

The unitary dose for the above discribed formulations will vary from 200 to 1000 mg of active ingredient.

Another type of pharmaceutical composition consists in suspensions or emulsions in which the active ingredient is present in concentrations varying from 20 to 50%, vehiculated in appropriate syrup excipients.

Some exemplificative formulations are reported hereinbelow.

A. Formulation in soft-gelatin capsules

Composition having 3 different dosages:			
Compound n. 3	1.000	750	500 mg
Vegetal oil	170	85	42.5

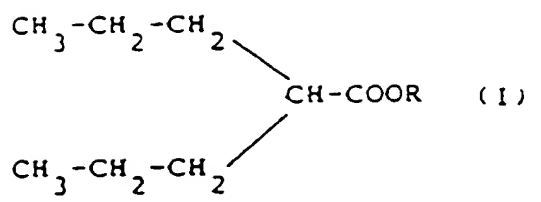
Formulation in hard-gelatin capsules

Composition having 2 different dosages:		
Compound n. 24	600	300 mg
Precipitated silica	46.2	23.1
Dipalmitostearic monoditriglicerides	50	25

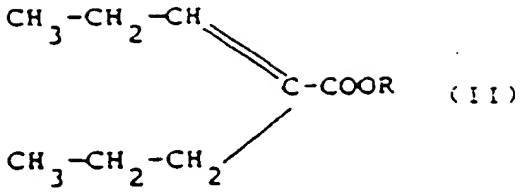
Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Compounds of general formulae



(I)



(II)

wherein R is an alkoxyalkyl, alkanoyloxyalkyl, aroyloxyalkyl, alkoxycarbonyloxyalkyl, aralkenoyloxyalkyl group, a mono- or bicyclic heterocycloalkyl group, which may be saturated or unsaturated and optionally substituted with a C_1-C_4 alkyl group or an oxo group; the above cited alkyl, alkoxyl and alkanoyl groups having straight or branched chain and containing 1 to 10 carbon atoms, with the proviso that, in compounds of general formula (I), R is not 1-ethoxycarbonyloxyethyl, pivaloyloxymethyl,pyrrolidin-1-yl-methyl

2. 2'-Acetoxyethyl 2-propyl-pentanoate;
1'-Pivaloyloxyethyl 2-propyl-pentanoate;
2'-Pivaloloxyethyl 2-propyl-pentanoate;
2'-Etoxycarbonyloxyethyl 2-propyl-pentanoate; (5-Methyl-1,3-dioxolene-2-oxo-4-yl)-methyl 2-propyl-pentanoate;
2'-(2,5-Dione-pyrrolidine-1-yl)-ethyl
2-propyl-pentanoate;
2-Propyl-pentanoyloxymethyl 2-propyl-pentanoate;
2'-(2-Propyl-pentanoyloxy)-ethyl
2-propyl-pentanoate, 2'-Benzoiloxyethyl (E)-2-propyl-2-pentenoate;
2'-Cinnamoyloxyethyl (E)-2-propyl-2-pentenoate;
2'-(3,4,5-trimethoxybenzoyl)-ethyl (E)-2-propyl-2-pentenoate;
2'-Acetoxyethyl (E)-2-propyl-2-pentenoate;
2'-Pivaloyloxyethyl (E)-2-propyl-2-pentenoate;
2'-Ethoxycarbonyloxyethyl(E)-2-propyl-2-pentenoate;
Pivaloyloxymethyl (E)-2-propyl-2-pentenoate;
Phthalidyl (E)-2-propyl-2-pentenoate;
Acetoxymethyl (E)-2-propyl-2-pentenoate;
1'-Pivaloyloxyethyl (E)-2-propyl-2-pentenoate;
(5-Methyl-2-oxo-1,3-dioxolene-4-yl)-methyl (E)-2-propyl-2-pentenoate;
2'-(2,5-Dione-1-pyrrolidine)-ethyl (E)-2-propyl-2-pentenoate;
2'-n-Butyloxyethyl (E)-2-propyl-2-pentenoate;
1'-Methoxymethylethyl (E)-2-propyl-2-pentenoate;
2'-Isopropyloxyethyl (E)-2-propyl-2-pentenoate;
2'-Methoxyethyl (E)-2-propyl-2-pentenoate;
2-Piridylmethyl (E)-2-propyl-2-pentenoate.

3. A process for preparing compounds (I) and (II), wherein the starting compound, i.e. valproic acid or (E)-2-valproenoic acid, is reacted with at least an equivalent molar amount of a haloderivative of formula RX, wherein R has the above defined meanings and X is chlorine or bromine, in an inert organic solvent, in the presence of appropriate amounts of an alkali substance and of a catalyst, at a temperature ranging from 0 °C to the solvent's boiling temperature.

4. A process according to claim 3, wherein potassium carbonate as the alkali substance and potassium iodide as the catalyst, are employed.

5. A process for preparing compounds (I) and (II), wherein R preferably represents a $-CH_2-O_2CCH(C_3H_7)_2$ or a $-(CH_2)_2-O_2CCH(C_3H_7)_2$, residue, said process consisting in reacting valproic acid or (E)-2-valproenoic acid in alkali aqueous solution with a dialkyl halide of the type $X-(CH_2)_n-X$ (wherein n = 1-5 and X = Cl, Br, I), in the presence of an appropriate catalyst, at a temperature ranging form 10 to 70 °C, for a period comprised between 1 and 24 hours.

6. A process according to claim 5, wherein 30% sodium hydroxide as the alkali substance and tetrabutylammonium hydrogenosulfate, as the catalyst, are employed.

7. Pharmaceutical compositions for oral administration, containing as the active ingredient one of the compounds of claims 1-2, in combination with a pharmaceutically acceptable excipient.

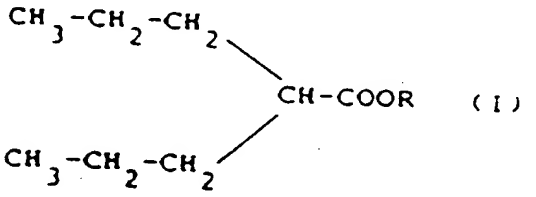
8. Pharmaceutical compositions according to claim 7, in unitary dosage forms consisting in soft-gelatin capsules or hard-gelatin capsules, containing 200 to 1.000 mg of active ingredient.

9. Pharmaceutical compositions according to claim 7, in form of suspensions or emulsions containing 20 to 50% of active ingredient.

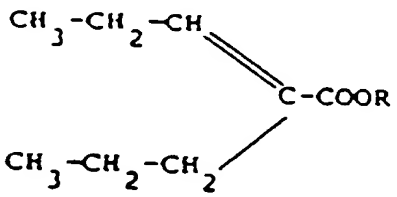
10. Pharmaceutical compositions according to claims 7-9 for the treatment of epileptic conditions.

Claims for the following Contracting States : ES, GR

1. A process for preparing compounds (I) and (II),



(I)



(II)

wherein R is an alkoxyalkyl, alkanoyloxyalkyl, aroyloxyalkyl, alkoxycarbonyloxyalkyl, aralkenoyloxyalkyl group, a mono- or bicyclic heterocycloalkyl group, which may be saturated or unsaturated and optionally substituted with a C_1-C_4 alkyl group or an oxo group; the above cited alkyl, alkoxyl and alkanoyl groups having straight or branched chain and containing 1 to 10 carbon atoms, with the proviso that, in compounds of general formula (I), R is not 1-ethoxycarbonyloxyethyl pivaloyloxymethyl or pyrrolidin-1-yl methyl, wherein the starting compound, i.e. valproic acid or (E)-2-valproenoic acid, is reacted with at least an equivalent molar amount of a haloderivative of formula RX, wherein R has the above defined meanings and X is chlorine or bromine, in an inert organic solvent, in the presence of appropriate amounts of an alkali substance and of a catalyst, at a temperature ranging from 0 °C to the solvent's boiling temperature.

2. A process according to claim 1, wherein potassium carbonate as the alkali substance and potassium iodide as the catalyst, are employed.

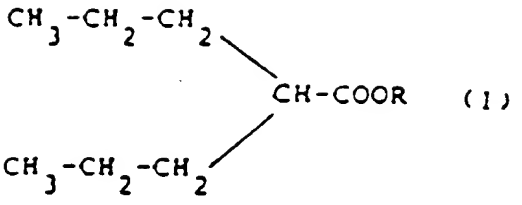
3. A process for preparing compounds (I) and (II), wherein R preferably represents a $-CH_2-O_2CCH(C_3H_7)_2$ or a $-(CH_2)_2-O_2CCH(C_3H_7)_2$, residue, said process consisting in reacting valproic acid or (E)-2-valproenoic acid in alkali aqueous solution with a dialkyl halide of the type $X-(CH_2)_n-X$ (wherein n = 1-5 and X = Cl, Br, I), in the presence of an appropriate catalyst, at a temperature ranging form 10 to 70 °C, for a period comprised between 1 and 24 hours.

4. A process according to claim 3, wherein 30% sodium hydroxide as the alkali substance and tetrabutylammonium hydrogenosulfate, as the catalyst, are employed.

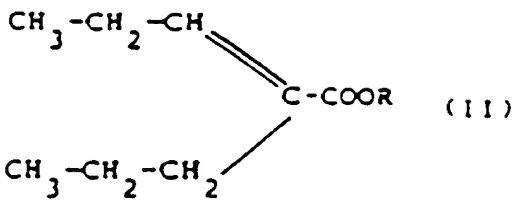
Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composés des formules générales :



(I)



(II)

dans lesquelles R représente un groupe alcoxyalkyle, alcanoyloxyalkyle, aroyloxyalkyle, alcoxycarbonyloxyalkyle, aralcénoyloxyalkyle, un groupe hétérocycloalkyle mono- ou bicyclique, qui peut être saturé ou insaturé et facultativement substitué par un groupe alkyle en C_1-C_4 ou un groupe oxo ; les groupes alkyle, alcoxyle et alcanoyle mentionnés ci-dessus ayant une chaîne droite ou ramifiée et contenant 1 à 10 atomes de carbone, à la condition que, dans les composés de la formule générale (I), R ne représente pas éthoxycarbonyloxy-1 éthyle, pivaloyloxyméthyle, pyrrolidinyl-1 méthyle.

2. Propyl-2 pentanoate d'acétoxy-2' éthyle ;
   - Propyl-2 pentanoate de pivaloyloxy-1' éthyle ;
   - Propyl-2 pentanoate de pivaloyloxy-2' éthyle ;
   - Propyl-2 pentanoate d'éthoxycarbonyloxy-2' éthyle ;
   - Propyl-2 pentanoate de (méthyl-5 dioxolène-1,3 oxo-2 yl-4)-méthyle ;
   - Propyl-2 pentanoate de (dione-2,5 pyrrolidinyl-1)-2' éthyle ;
   - Propyl-2 pentanoate de propyl-2 pentanoyloxyméthyle ;
   - Propyl-2 pentanoate de (propyl-2 pentanoyloxy)-2' éthyle;
   - (E)-propyl-2 pentén-2 oate de benzoyloxy-2' éthyle ;
   - (E)-propyl-2 pentén-2 oate de cinnamoyloxy-2' éthyle ;
   - (E)-propyl-2 pentén-2 oate de (triméthoxy-3,4,5 benzoyl)-2' éthyle ; (E)-propyl-2 pentén-2 oate d'acétoxy-2' éthyle ;
   - (E)-propyl-2 pentén-2 oate de pivaloyloxy-2' éthyle ;
   - (E)-propyl-2 pentén-2 oate d'éthoxycarbonyloxy-2' éthyle;
   - (E)-propyl-2 pentén-2 oate de pivaloyloxyméthyle ;
   - (E)-propyl-2 pentén-2 oate de phtalidyle ;
   - (E)-propyl-2 pentén-2 oate d'acétoxyméthyle ;
   - (E)-propyl-2 pentén-2 oate de pivaloyloxy-1' éthyle ;
   - (E)-propyl-2 pentén-2 oate de (méthyl-5 oxo-2 dioxolène-1,3 yl-4)-méthyle ;
   - (E)-propyl-2 pentén-2 oate de (dione-2,5 pyrrolidine-1)-2' éthyle ;
   - (E)-propyl-2 pentén-2 oate de n-butyloxy-2' éthyle ;
   - (E)-propyl-2 pentén-2 oate de méthoxyméthyl-1' éthyle ;
   - (E)-propyl-2 pentén-2 oate d'isopropyloxy-2' éthyle ;
   - (E)-propyl-2 pentén-2 oate de méthoxy-2' éthyle ;
   - (E)-propyl-2 pentén-2 oate de pyridyl-2 méthyle.

3. Procédé de fabrication de composés (I) et (II) dans lequel on fait réagir le composé de départ, à savoir l'acide valproïque ou l'acide (E)-valproénoïque-2, avec au moins une quantité molaire équivalente d'un dérivé halogéné de la formule RX, dans laquelle R a les significations mentionnées ci-dessus et X représente chlore ou brome, dans un solvant organique inerte, en présence de quantités appropriées d'une substance alcaline et d'un catalyseur, à une température se situant dans la plage de 0 °C à la température d'ébullition du solvant.

4. Procédé selon la revendication 3, dans lequel on emploie du carbonate de potassium comme substance alcaline et de l'iodure de potassium comme catalyseur.

5. Procédé de fabrication de composés (I) et (II), dans lesquels R représente, de préférence, un reste $-CH_2-O_2CCH(C_3H_7)_2$ ou $-(CH_2)_2-O_2CCH(C_3H_7)_2$, ledit procédé consistant à faire réagir de l'acide valproïque ou de l'acide (E)-valproénoïque-2 dans une solution aqueuse alcaline avec un halogénure de dialkyle du type $X-(CH_2)_n-X$ (où n = 1-5 et x = Cl, Br, I), en présence d'un catalyseur approprié, à une température se situant dans la plage de 10 à 70 °C, pendant une période de temps comprise entre 1 à

24 heures.

6. Procédé selon la revendication 5, dans lequel on emploie de l'hydroxyde de sodium à 30% comme substance alcaline et de l'hydrogénosulfate de tétrabutylammonium comme catalyseur.

7. Compositions pharmaceutiques pour une administration orale, contenant, en tant qu'ingrédient actif, l'un des composés des revendications 1-2, en combinaison avec un excipient pharmaceutiquement acceptable.

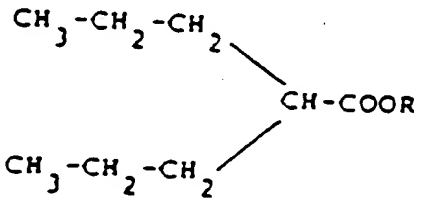
8. Compositions pharmaceutiques selon la revendication 7, sous des formes de dosage unitaires, consistant en capsules de gélatine molle ou capsules de gélatine dure, contenant 200 à 1000 mg d'ingrédient actif.

9. Compositions pharmaceutiques selon la revendication 7, sous la forme de suspensions ou d'émulsions contenant 20 à 50% d'ingrédient actif.

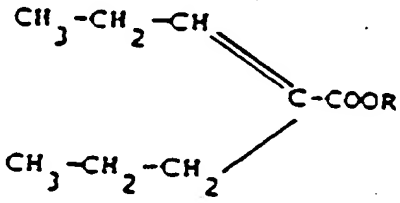
10. Compositions pharmaceutiques selon les revendications 7-9 pour le traitement des états épileptiques.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de fabrication de composés (I) et (II),



(I)



(II)

dans lesquelles R représente un groupe alcoxyalkyle, alcanoyloxyalkyle, aroyloxyalkyle, alcoxycarbonyloryalkyle, aralcénoyloxyalkyle, un groupe hétérocycloalkyle mono- ou bicyclique, qui peut être saturé ou insaturé et facultativement substitué par un groupe alkyle en C_1-C_4 ou un groupe oxo ; les groupes alkyle, alcoxyle et alcanoyle mentionnés ci-dessus ayant une chaîne droite ou ramifiée et contenant 1 à 10 atomes de carbone, à la condition que, dans les composés de la formule générale (I), R ne représente pas éthoxycarbonyloxy-1 éthyle, pivaloyloxyméthyle ou pyrrolidinyl-1 méthyle,
dans lequel on fait réagir le composé de départ, à savoir l'acide valproïque ou l'acide (E)-valproénoïque-2, avec au moins une quantité molaire équivalente d'un dérivé halogéné de la formule RX, dans laquelle R a les significations mentionnées ci-dessus et X représente chlore ou brome, dans un solvant organique inerte, en présence de quantités appropriées d'une substance alcaline et d'un catalyseur, à une température se situant dans la plage de 0 °C à la température d'ébullition du solvant.

2. Procédé selon la revendication 1, dans lequel on emploie du carbonate de potassium comme substance alcaline et de l'iodure de potassium comme catalyseur.

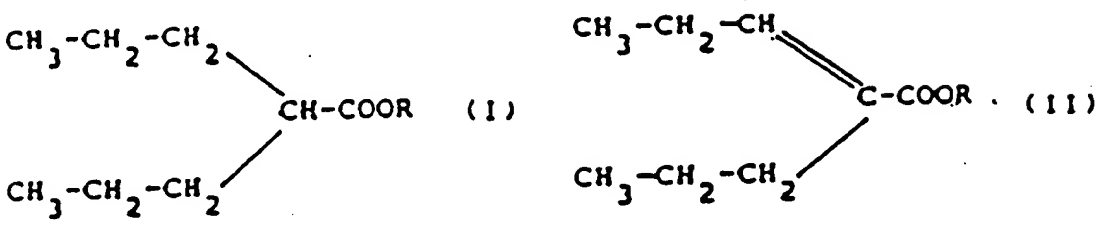
3. Procédé de fabrication des composés (I) et (II), dans lesquels R représente, de préférence, un reste $-CH_2-O_2CCH(C_3H_7)_2$ ou $-(CH_2)_2-O_2CCH(C_3H_7)_2$, ledit procédé consistant à faire réagir de l'acide valproïque ou de l'acide (E)-valproénoïque-2 dans une solution aqueuse alcaline avec un halogénure de dialkyle du type $X-(CH_2)_n-X$ (où n = 1-5 et x = Cl, Br, I), en présence d'un catalyseur approprié, à une température se situant dans la plage de 10 à 70 °C, pendant une période de temps comprise entre 1 à 24 heures.

4. Procédé selon la revendication 3, dans lequel on emploie de l'hydroxyde de sodium à 30% comme substance alcaline et de l'hydrogénosulfate de tétrabutylammonium comme catalyseur.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindungen der allgemeinen Formeln



worin R ein Alkoxyalkyl-, Alkanoyloxyalkyl-, Aroyloxyalkyl-, Alkoxycarbonyloxyalkyl-, Aralkenoyloxyalkylrest oder ein mono- oder bicyclischer Heterocycloalkylrest ist, der gesättigt oder ungesättigt sein kann und gegebenenfalls mit einem C_1-C_4-Alkylrest oder einem Oxorest substituiert ist, wobei die angegebenen Alkyl-, Alkoxyl- und Alkanoylreste eine gerade oder verzweigte Kette aufweisen und 1 bis 10 Kohlenstoffatome enthalten mit der Maßgabe, daß in Verbindungen der allgemeinen Formel (I) der Rest R nicht für 1-Ethoxycarbonyloxyethyl, Pivaloyloxymethyl oder Pyrrolidin-1-yl-methyl steht.

2. 2'-Acetoxyethyl-2-propyl-pentanoat,
1'-Pivaloyloxyethyl-2-propyl-pentanoat,
2'-Pivaloyloxyethyl-2-propyl-pentanoat,
2'-Ethoxycarbonyloxyethyl-2-propyl-pentanoat, (5-Methyl-1,3-dioxolen-2-oxo-4-yl)-methyl 2-propyl-pentanoat,
2'-(2,5-Dion-pyrrolidin-1-yl)-ethyl-2-propyl-pentanoat,
2-Propyl-pentanoyloxymethyl-2-propyl-pentanoat,
2'-(2-Propyl-pentanoyloxy)-ethyl-2-propyl-pentanoat, 2'-Benzoyloxyethyl-(E)-2-propyl-2-pentenoat,
2'-Cinnamoyloxyethyl-(E)-2-propyl-2-pentenoat,
2'-(3,4,5-Trimethoxybenzoyl)-ethyl-(E)-2-propyl-2-pentenoat,
2'-Acetoxyethyl-(E)-2-propyl-2-pentenoat,
2'-Pivaloyloxyethyl-(E)-2-propyl-2-pentenoat,
2'-Ethoxycarbonyloxyethyl-(E)-2-propyl-2-pentenoat,
Pivaloyloxymethyl-(E)-2-propyl-2-pentenoat, Phthalidyl-(E)-2-propyl-2-pentenoat, Acetoxymethyl-(E)-2-propyl-2-pentenoat,
1'-Pivaloyloxyethyl-(E)-2-propyl-2-pentenoat, (5-Methyl-2-oxo-1,3-dioxolen-4-yl)-methyl-(E)-2-propyl-2-pentenoat,
2'-(2,5-Dion-1-pyrrolidin)-ethyl-(E)-2-propyl-2-pentenoat,
2'-n-Butyloxyethyl-(E)-2-propyl-2-pentenoat,
1'-Methoxymethylethyl-(E)-2-propyl-2-pentenoat,
2'-Isopropyloxyethyl-(E)-2-propyl-2-pentenoat,
2'-Methoxyethyl-(E)-2-propyl-2-pentenoat,
2-Pyridylmethyl-(E)-2-propyl-pentenoat.

3. Verfahren zur Herstellung der Verbindungen (I) und (II), worin die Ausgangsverbindung, d. h. Valproesäure oder (E)-2-Valproensäure mit mindestens einer äquivalenten molaren Menge eines Halogenderivates der Formel RX, worin R die oben angegebene Bedeutung hat und X für Chlor oder Brom steht, in einem inerten organischen Lösungsmittel in Gegenwart von geeigneten Mengen einer Alkali-Substanz und eines Katalysators bei einer Temperatur im Bereich von 0 °C bis zur Siedetemperatur des Lösungsmittels umgesetzt wird.

4. Verfahren nach Anspruch 3, worin Kaliumcarbonat als Alkali-Substanz und Kaliumiodid als Katalysator eingesetzt werden.

5. Verfahren zur Herstellung von Verbindungen der allgemeinen Formeln (I) und (II), worin R vorzugsweise einen Rest $-CH_2-O_2CCH(C_3H_7)_2$ oder $-(CH_2)_2-O_2CCH(C_3H_7)_2$ darstellt, wobei das Verfahren darin besteht, daß Valproesäure oder (E)-2-Valproensäure in einer alkalischen wässrigen Lösung mit einem

Dialkylhalogenid des Typs $X-(CH_2)_n-X$ (worin n = 1-5 und x = Cl, Br, J ist) in Gegenwart eines geeigneten Katalysators bei einer Temperatur im Bereich von 10 bis 70 °C für eine Zeitdauer von 1 bis 24 Stunden umgesetzt wird.

6. Verfahren nach Anspruch 5, worin 30 %iges Natriumhydroxid als die Alkali-Substanz und Tetrabutylammoniumhydrogensulfat als Katalysator eingesetzt werden.

7. Pharmazeutische Zusammensetzungen für die orale Verabfolgung, enthaltend als aktiyen Bestandteil eine der Verbindungen gemäß Anspruch 1 bis 2 in Kombination mit einem pharmazeutisch verträglichen Excipienten.

8. Pharmazeutische Zusammensetzungen nach Anspruch 7 in Einheits-Dosierungsformen, bestehend aus Weich-Gelatine-Kapseln oder Hart-Gelatine-Kapseln, welche 200 bis 1.000 mg des aktiven Bestandteils enthalten.

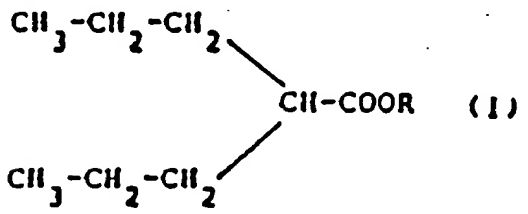
9. Pharmazeutische Zusammensetzungen nach Anspruch 7 in Form von Suspensionen oder Emulsionen, welche 20 bis 50 % des aktiven Bestandteils enthalten.

10. Pharmazeutische Zusammensetzungen nach den Ansprüchen 7 bis 9 zur Behandlung von epileptischen Zuständen.

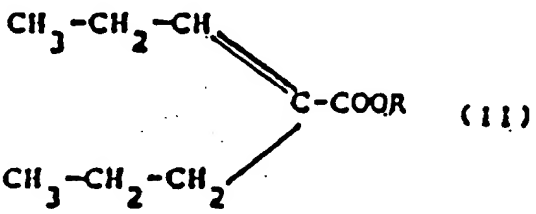
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung von Verbindungen (I) und

(II)



(I)



(II)

worin R ein Alkoxyalkyl-, Alkanoyloxyalkyl-, Aroyloxyalkyl-, Alkoxycarbonyloxyalkyl-, Aralkenoyloxyalkyl-Rest oder ein mono- oder bicyclischer Heterocycloalkyl-Rest ist, der gesättigt oder ungesättigt sein kann und gegebenenfalls mit einem C_1-C_4-Alkylrest oder einem Oxorest substituiert ist, wobei die angegebenen Alkyl-, Alkoxyl- und Alkanoylgruppen eine gerade oder verzweigte Kette und 1 bis 10 Kohlenstoffatome aufweisen mit der Maßgabe, daß in Verbindungen der allgemeinen Formel (I) der Rest R nicht für 1-Ethoxycarbonyloxyethyl, Pivaloyloxymethyl oder Pyrrolidin-1-yl-methyl steht, worin die Ausgangsverbindung, d. h. Valproesäure oder (E)-2-Valproensäure mit mindestens einer äquivalenten molaren Menge eines Halogenderivates der allgemeinen Formel RX, worin R die oben angegebene Bedeutung besitzt und X für Chlor oder Brom steht, in einem inerten organischen Lösungsmittel in Gegenwart von angemessenen Mengen einer Alkali-Substanz und eines Katalysators bei einer Temperatur im Bereich von 0 °C bis zur Siedetemperatur des Lösungsmittels umgesetzt wird.

2. Verfahren nach Anspruch 1, worin Kaliumcarbonat als Alkali-Substanz und Kaliumiodid als Katalysator eingesetzt werden.

3. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel (I) und (II), worin R vorzugsweise einen Rest $-CH_2-O_2CCH(C_3H_7)_2$ oder $-(CH_2)_2-O_2CCH(C_3H_7)_2$ bedeutet, wobei das Verfahren darin besteht, daß Valproesäure oder (E)-2-Valproensäure in alkalischer wässriger Lösung mit einem Dialkylhalogenid der Formel $X-(CH_2)_n-X$ (worin n = 1-5 bedeutet und X = Cl, Br oder J ist), in Gegenwart eines entsprechenden Katalysators bei einer Temperatur im Bereich von 10 bis 70 °C für einen Zeitraum von 1 bis 24 Stunden umgesetzt wird.

4. Verfahren nach Anspruch 3, worin 30 %iges Natriumhydroxid als Alkali-Substanz und Tetrabutylammo-

niumhydrogensulfat als Katalysator eingesetzt werden.